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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,948	05/30/2001	Brian Maiorella	PP00693.104	9747

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EXAMINER

LIU, SAMUEL W

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 03/25/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/867,948

Applicant(s)

MAIORELLA ET AL.

Examiner

Samuel W Liu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) none is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 2-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

The response filed January 29 2003 (Paper No. 6) as to cancellation of claim 2, amendment of claims 1, 3 and 6, and addition of new claim 37 have been entered. Applicant's submission of the revised drawings for Figure 1 filed 29 January 2003 (Paper No. 7) is acknowledged.

The following pending claims 1 and 3-6 are examined in this Office action.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Terminal Disclaimer

The terminal disclaimer filed 29 January 2003 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Pat. No. 6238891 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-6 are rejected under 35 U.S.C. 102 (b) as being anticipated by Rupp, R. G. *et al.* (GB 2153830, published 29 August 1985).

Rupp *et al.* teach a method of improving protein production in animal cell culture under an environment of solute stress (*i.e.*, amino acid mediated hypertonicity) of the culture medium comprising: (i) growing the animal cells, *i.e.*, hybridoma, to a maximum density (see page 3, lines 7-9), as applied to application claim 1 item *a*); (ii) increasing the tonicity (*i.e.*, solute stress) by incrementally addition of excess solutes *i.e.*, amino acids (see claims 2-3, abstract, and page 3, lines 30 -33 and lines 42-43) so as to promote the hybridoma cell growth *via* increasing cell growth rate (see page 1, line 1-5 , and Figure at page 6, lines 56-59) as hypertonic medium may have negative effect on cell growth (see page 6, line 58-59), as applied to the limitation of claim 1 item *b*); and (iii) monitoring the protein production under maximum of cell growth in the culture medium being maintained to a desired solute stress condition, (see claim 3, page 3, lines 7-9 and 16-18 and Example 1), wherein the protein-production is monitored by harvesting protein produced by the cells (see page 3, lines 19-20) and the different solute stress measured as osmolarity results in different protein yield, *i.e.*, $\mu\text{g/ml}$ of produced antibody (see Table 4 at page 7), as applied to claim 1 item *c*); and (iv) selecting optimal combination of cell growth and product expression (see page 2, lines 4-6, and Table 4 showing that the peak of antibody production is under amino acid-mediated osmolarity ~ 360 mOsmoles, and also see claims 1 and 4-5), as applied to claim 1 item *d*) of the instant application.

Also, Rupp *et al.* teach the cell culture is mammalian cell culture (see the patent claims 1 and 6) expressing monoclonal antibody (see page 1, line 45); the cell is hybridoma cell producing IgG antibody (see the patent claims 1-13, Example 1, and page 3, line 34); and monoclonal antibody is generated from mouse or human hybridoma (see the bridging pages 7-8), as applied to claims 3-6 of the instant application.

Response to the rejection under 35 USC 102

The response filed 29 January 2003 asserts that Rupp *et al.* do not seek to stress their cultured cells (*i.e.*, apply solute stress to the cells), the Rupp *et al.* objective is to increase protein production without having adverse impact on cell growth or cell viability, and Rupp teaches retaining cell viability and rate of cell mitosis (see page 7). The applicants' argument is unpersuasive because: (i) Rupp *et al.* do teach stressing the cultured cells by using that hypertonic medium generated by addition of excess amino acids as solutes (see the patent claims 1-3, page 4, line 1, and page 2, lines 7-8). (ii) Rupp *et al.* address the issue regarding adverse effect of hypertonic medium (see page 6, lines 58-59) and teach an optional osmolarity (*i.e.*, solute stress) for maximum product production *i.e.*, over the optimal level of solute stress, there is an adverse effect on antibody production (see especially group B data of Table 4 at page 7); and, (iii) Rupp *et al.* teach a method of improving or promoting protein production, especially antibody production, in animal cultures rather than targets simply on increasing cell viability (see page 1, lines 64-65, claims 1-3, abstract, and Table 4 data).

The response asserts that Rupp *et al.* never teach or suggest that the medium has to be made sufficiently hypertonic such that stress is induced on the cells and cell growth is inhibited, and that the Rupp *et al.* patent do not propose or even suggest that one can determine the optimal level of product expression by identifying a solute level in the culture medium for maximal protein expression (see page 8, the first paragraph). The applicants' argument is found unpersuasive.

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Rupp *et al.* teach optimization of amino acid-mediated osmolarity for maximal antibody production (see claims 1-5 and Table 4 data, which show that the maximum level of the production is under amino acid solute stress of osmolarity ~ 360 mOsmoles), and teach when reaching a certain level of hypertonicity, the hybridoma cell growth is impaired (see Table 4, group B data, and page 6, lines 58-59). The experimental data of Table 4 suggest that the optimal solute stress (herein expressed as osmolarity) needs to be determined because too high level of the stress would decrease product production (see average antibody production level [$\mu\text{g/ml}$] of the test groups B: 67.1, 7.5 and 70.6); thereby, Rupp *et al.* determine the optimal level of stress solute stress being ~ 360 mOsmoles (see the patent claim 5).

Also, the response discuss the issue as to selection of maximum osmolarity for optimal product production, asserts that the Rupp *et al.* teaching does not reflect significant change in antibody synthesis when hypertonic cell cultures are compared, and question that in the Rupp patent, solute stress had not been reached at 400 mOsmoles, *i.e.*, maximum osmolarity; thus, applicants infer that the Rupp data do not constitute solute stress (see page 8, the second paragraph, and page 9, the first paragraph). The applicants' argument is unpersuasive because the Rupp *et al.* patent does show a remarked change in the antibody production by comparison of the stressed cell culture 390 indicated by "o" and culture 396 indicated by "Δ" with the unstressed culture 397 indicated by "◊" (see Figure 3, the inserted legends of Figure 1, and page 1, lines 57-65) (for description of cultures 390, 396 and 397 see page 7, lines 1-12), and because Rupp *et al.* teaching amino acid-mediated hypertonicity (increased osmolarity) of the culture medium ~ 340-450 mOsmoles (see page 1, lines 53-54) in comparison to isotonic osmolarity ~ 280-300 mOsmoles (see page 3, lines 27-28 of the current application), and Rupp *et al.* present the data

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showing the solute stress of 400 mOsmoles where the maximum production is or is not reached, depending the cell cultures (see Table 4). Thus, applicants' argument is unpersuasive.

Further, the response infers that Rupp *et al.* reference does not teach every element of the current application (see page 9, the second paragraph). The applicants' argument is unpersuasive because of the reasons set forth *supra*.

Claim Rejection –Obviousness Type Double Patenting

In view of the filed and approved terminal disclaimer the rejection is withdrawn.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.



Samuel W. Liu, Ph.D.

March 19, 2003



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